Pathophysiology of Atherosclerosis

Introduction

This lesson is the first in the coronary artery disease (CAD) island. It is the culmination of all the other Cardiac islands. We assume that you have already completed the rest of the Cardiac modules and will not give you space or time to catch up. To comprehend this island requires the components of hemodynamics (atherosclerosis is a pathology of blood vessels), the heart as a muscle and a pump, the flow of blood and the two-heart model, and the electrical conduction system.

This first lesson is not about CAD at all, but rather the pathophysiology of the **atherosclerotic plaque** that defines ALL arterial vascular disease. CAD is atherosclerosis of the arteries of the heart; [any organ] vascular disease is atherosclerosis of the arteries of the [corresponding organ]. In atherosclerosis, a plaque forms within the lumen of medium-to-large-sized blood vessels. The plaque forms over decades, gradually narrowing the lumen of the artery in which it is growing. In this lesson, we follow the path from a normal, healthy artery to a symptomatic plaque. We explore how the plaque forms and what that does to the blood flow in the artery in which it is forming. The subsequent lessons in the CAD island are about chronic ischemic heart disease caused by atherosclerosis and acute rupture and thrombosis caused by unstable lesions.

We start by clarifying similar-sounding words that get people tripped up, then dive into plaque formation. The atherosclerotic plaque is a product of atherosclerosis. Then, we progress from endothelial dysfunction (a vague process not yet elucidated by medical science) to eventual rupture and thrombosis (well elucidated and often fatal should it occur in the coronary arteries).

Clarification on Sclerosis

The reason we introduced hyaline arteriolosclerosis and hyperplastic arteriolosclerosis in the first island (Hemodynamics), seemingly out of context, was to prepare you for this discussion. You've seen hyaline arteriolosclerosis (chronic hypertension) and hyperplastic arteriolosclerosis (malignant hypertension) before. Therefore, we can use words that sound or look similar-ish, and you won't be confused by them. We are going to obnoxiously overstate the disease names so that you do not confuse them. This section is designed to identify **what you can ignore** for the rest of the CAD island.

Arterio-sclerosis (artery-o-sclerosis, arteriosclerosis) is the single most useless and unhelpful term. It literally means hardening of the arteries and is an **umbrella term** for any kind of arterial sclerosis, no matter the size of the vessel or the underlying etiology. **Never say arteriosclerosis** because it is a **generic term** for arterial wall thickening and loss of elasticity that conveys **nothing of import**. There are multiple subtypes, which we enumerate here. Arteriosclerosis can be Mönckeberg, hyaline arteriolosclerosis, hyperplastic arteriolosclerosis, or atherosclerosis. You can see how similarly the words are spelled and how much they sound alike, which is why we are running this exercise now.

Mönckeberg medial sclerosis is a subtype of ~~arteriosclerosis~~ *useless umbrella term* caused by **calcifications** in the tunica media of medium-sized muscular arteries. The calcifications do not encroach on the lumen of the vessel, but rather they are found within the tunica media. This calcification occurs over time and so is seen in people over the age of 50. This plays a role in how blood pressure changes as people age, resulting in an unreliable brachial ankle index, and is not associated with disease. You will not see it again in the Basic Sciences curriculum. It isn't that it isn't important, it just doesn't lead to a disease state, so it is unimportant in the Basic Sciences.

You saw **hyaline arteriolosclerosis** (arteriole-o-sclerosis) when we talked about essential hypertension. That is microvascular disease that affects small arteries and arterioles. The risk factors for this type of histological change are chronic hypertension and diabetes. It is a relevant cause of hardening of the

small arteries (arteriosclerosis) and causes tissue hypoxemia leading to organ failure over a long period. In this lesson, it is irrelevant because it is not atherosclerosis, which is macrovascular disease that affects large and medium arteries.

You also saw **hyperplastic arteriolosclerosis** (arteriole-o-sclerosis), which we redefined as the histological pattern of "malignant hypertension," indicative of long-standing severe hypertension. This, like hyaline arteriolosclerosis, is a disease of the small vessels and unrelated to atherosclerosis.

None of the above are CAD. Atherosclerosis is CAD. Atherosclerosis is **all vascular disease**, meaning that because all organs require blood vessels to function, and atherosclerosis can occur in any blood vessel, any organ can be affected. **Atherosclerosis** (atheroma-inducing-sclerosis) is **macrovascular** arteriosclerosis and the most clinically relevant arteriolosclerosis. From this point forward, "sclerosis" will only be used in the context of atherosclerosis, wherein a growing plaque causes progressive narrowing of an artery's lumen.

Atherosclerosis is the development of cholesterol plaques in **large elastic arteries** (e.g., aorta, carotid, iliacs) and **medium muscular arteries** (the named arteries, such as coronary and popliteal). The plaque, called an **atheroma**, grows within the **tunica intima**. Over time, the plaque grows into the lumen, narrowing the lumen and limiting or blocking blood flow. This is ischemic vascular disease. Not only does the plaque contribute to chronic ischemia, but it also has the potential to rupture, superimposing a thrombus. When anyone discusses "vascular disease" or denotes "vasculopathy," they are referring to atherosclerosis somewhere in any artery.

We happen to be in the Cardiac module. We happen to be discussing CAD, which is atherosclerosis of the coronary arteries. It is important to call CAD out on its own because it is the cause of so much death. But any organ that has arteries (all organs) can suffer the effects of atherosclerosis. The symptoms are dependent on the vessels involved, but all "vascular disease" is synonymous with atherosclerosis.

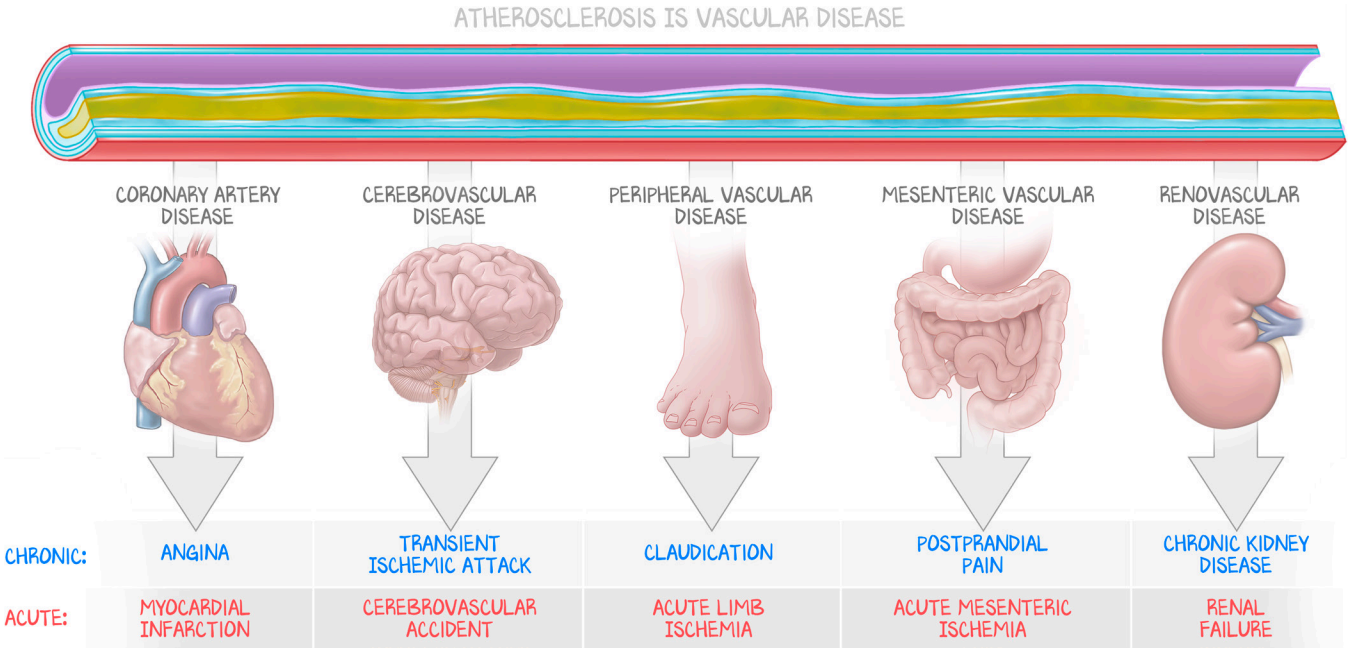

Figure 1.1: Atherosclerosis Is Vascular Disease
Atherosclerosis is the underlying cause of CAD, peripheral vascular disease, and cerebrovascular disease. When atherosclerosis occludes 70% of the lumen, symptoms arise. Patients experience angina (chest pain) if the plaque is in the heart, claudication (leg pain) if the plaque is in the arteries of the leg, and transient ischemic attacks if the plaque is in the brain. Plaque rupture and thrombus formation cause acute occlusion of the vessel, which transforms the chronic disease into an acute one—myocardial infarction if in the heart, acute limb ischemia if in the leg, and stroke if in the brain.

Atherosclerotic Plaque Overview: Anatomy

Flash forward: an atherosclerotic plaque has already developed within the tunica intima of some large artery. We will explore how this happens over the course of this lesson, but we want to start where the story ends. A fully developed, symptomatic plaque is made of two parts: a necrotic lipid core and a fibrous cap. A dangerously thrombogenic (causes a clot to form) **necrotic lipid core** made of free cholesterol, phospholipids, necrotic foam cells, and oxidized low-density lipoprotein (LDL) particles is at the heart of atherosclerosis. The blood vessel has responded—the necrotic core is surrounded by a **fibrous cap** consisting of vascular smooth muscle cells (VSMC; which have migrated from the tunica media into the intima) and the extracellular matrix proteins they make. Both the lipid core and fibrous cap are beneath the endothelial cells, but above the inner elastic lamina, within the tunica intima. The problem is how much the necrotic plaque and the fibrous cap compromise the lumen.

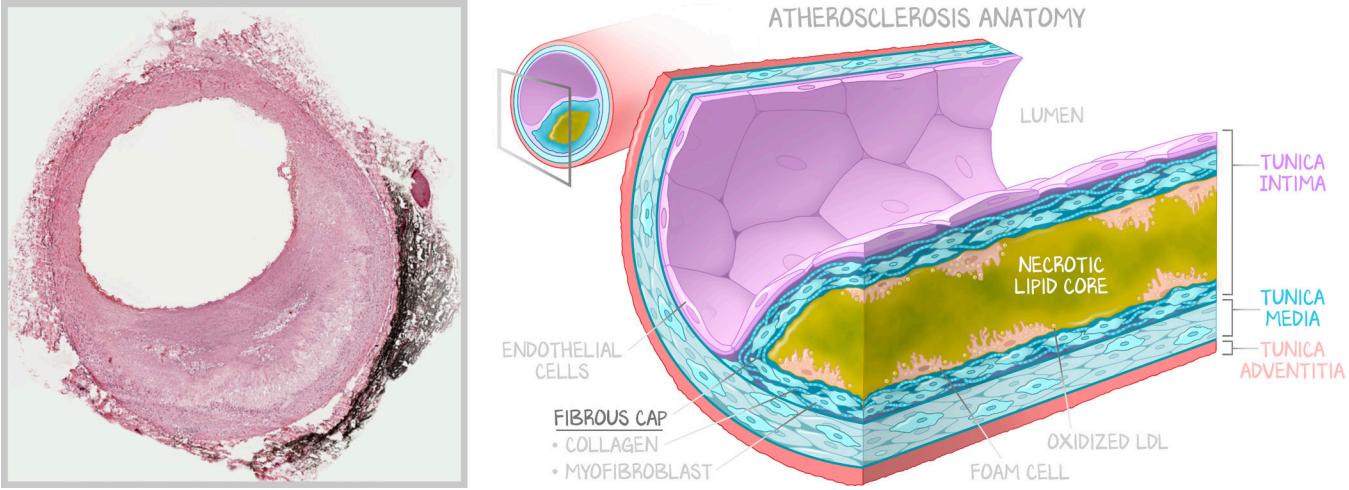

Figure 1.2: Atherosclerosis Anatomy
The histology on the left provides context for the illustration on the right. The artery is large, but its lumen not fully open. There is a necrotic lipid core (lighter pink) between the fibrous cap (dark pink near lumen) and the tunica media (dark pink that encompasses the entire circumference of the vessel). The illustration makes it clear that the endothelium remains the same—one cell thick—but the tunica intima, above the inner elastic lamina, has a large lipid core with a fibrous cap made of vascular smooth muscle cells. The lesion causes an eccentric stenosis of the lumen, as the lipid core is formed only on side of the vessel.

We are about to tell a long story. A story with stopping points, but one of a disease that is continuous, gradual, insidious, and long. We want you to pay attention to the lipid core in the tunica intima covered by a fibrous cap, formed by the tunica media's VSMCs that have migrated into the tunica intima, and what the plaque does to **obstruct blood flow**. You have read essentially the same message twice, once before and once after the figure. It may seem repetitive and tedious, but it is purposeful.

The process of atherosclerosis occurs over decades. The earliest evidence of lipid cores is found in the teenage years. Clinical symptoms of atherosclerosis generally do not appear until the sixth or seventh decade of life. The development of symptomatic vascular disease due to atherosclerosis depends on many risk factors. Some are modifiable and what we pursue in treating disease, to delay or reverse the atherosclerosis. Some are nonmodifiable and identify patients we should pay closer attention to and treat more aggressively compared to those with modifiable risk factors.

NONMODIFIABLE RISK FACTORS	MODIFIABLE RISK FACTORS
Genetic abnormalities (hypertriglyceridemia) Family history Increasing age (M > 45, F > 55) Age is the single largest risk factor	Hyperlipidemia Hypertension Cigarette smoking Diabetes Obesity

Table 1.1: Atherosclerosis Risk Factors

Initiation of Plaque Formation: Normal Endothelium Goes Bad

Medical science has elucidated experimental models in which atherosclerosis is induced by endothelial injury. Medical science knows what causes endothelial injury and accelerates the development of symptomatic plaques—the modifiable risk factors for vascular disease. However, medical science has not yet clearly elucidated what initiates the original endothelial dysfunction, as early atherosclerotic lesions in humans begin at sites of intact endothelium and in the absence of risk factors. In the next lesson, we will approach this metaphorically in response to the underlying pathogenesis and pharmacology of atherosclerosis. Here, we review what is known and keep the message accurate and scientific.

Because early atherosclerotic lesions have been found during autopsies of otherwise healthy teenagers without atherosclerosis risk factors (they died from trauma, for example), the lesions apparently begin in healthy endothelium at a very young age. In animal studies, experimental models can induce endothelial injuries that both start and accelerate atherosclerotic plaque formation. Dysfunctional endothelial cells exhibit the features of endothelial injury—increased permeability, enhanced leukocyte adhesion, and altered gene expression. But what causes the initial endothelial injury that starts the process? This is proposed only as a theory, but it sounds like a pretty good one: *hemodynamic disturbances initiate endothelial dysfunction; both hemodynamic disturbances and LDL cholesterol perpetuate it*.

Hemodynamic disturbances exist at branch points in arteries, where there are disturbed flow patterns, leading to turbulence. Turbulence is nonlaminar flow. The sequence of intracellular molecular and genetic changes is not well elucidated, but because atherosclerosis develops at these branches of nonlaminar flow, turbulent flow must contribute to the initial endothelial dysfunction. Turbulent flow weakens the endothelium at branch points. Turbulent flow also perpetuates the growth of the plaque and is the impetus of its rupture. We know that a severely stenosed lesion (> 70% of the lumen occupied) is significantly more likely to rupture than a less-stenosed one (less than 70% occupied). As we will discuss, it has to do with the relative strength of the fibrous cap, but the key feature of that 70% number is extremely turbulent flow through the lumen at that plaque. **Branch points** cause hemodynamic disturbances. Hemodynamic disturbances cause endothelial dysfunction. Endothelial dysfunction leads to plaque formation. Plaque formation **worsens hemodynamic disturbances**. And so the cycle continues.

Lipids are known to be atherogenic, as seen in the genetic disease of familial hypercholesteremia, wherein a defective LDL receptor, and therefore deficient hepatic uptake of LDL, can precipitate myocardial infarctions before age 20. Excess circulating LDL particles carrying cholesterol are deposited into the intima. They deposit more readily where the endothelium is leaky. Early cholesterol deposition exacerbates endothelial dysfunction by increasing local reactive oxygen species. The lipoproteins accumulate in the intima, where they aggregate and are oxidized by those free radicals. More endothelial dysfunction. And so the cycle continues. **LDL** is the main offender. **LDL cholesterol accumulates in areas afflicted by hemodynamic disturbances.**

Branch points, modifiable risk factors, and elevated LDL levels exacerbate and accelerate atherosclerosis. Atherosclerosis begins with turbulent flow letting in LDL. LDL accumulates until the immune system notices. Once it notices, an unending cycle of failure creates the plaque and keeps it growing. This cycle is discussed in the next section.

Progression of the Atherosclerotic Plaque, Step by Step

We will focus on what you need to know to understand the formation of an atherosclerotic plaque and the management of atherosclerosis. There is much more to this, but we do not want you to be bogged down by extraneous detail. If this seems too simple (it isn't simple, but has been simplified), it is because we are intentionally giving you only the information that matters. There is a continuous progression of plaque development, but we chose six snapshots, each an instance of what a plaque looks like over sixty years. We want you to learn them as stages, but we also want you to know that these are not discrete phases; we've merely categorized them into phases to communicate what you need to know.

Fatty streak (lipid core, no necrosis), atheroma (fatty streak with necrosis), arterial remodeling (the large artery trying), complex atheroma through stable plaque, stable critical stenosis, unstable plaque, and finally, rupture and thrombosis. These are the words you will use over the next five lessons.

Formation of the fatty streak. An artery starts as normal, without a plaque or the propensity to form one. That artery is subjected to chronic endothelial stress—hemodynamic disturbances at branch points. This chronic stress increases the vascular permeability (leaky endothelium), allowing LDL particles into the intima, where they are oxidized. These oxidized particles form a **lipid core**. In small amounts, these particles go unnoticed. But over time, the lipid core grows. When the lipid core gets big enough to be noticed, the endothelial cells cry out for help. "Crying out for help" mirrors the vascular changes of inflammation: increased permeability and increased leukocyte adhesion (Immunology #4: *Innate Immune System*). This process is slow, it takes decades, and only after the fatty streak is noticed by the immune system does the vessel respond.

Atheroma formation. Monocytes emigrate from the lumen of the vessel into the tunica intima, where they differentiate into **macrophages**. Macrophages phagocytose the **free cholesterol** and **oxidized LDL** in the core. It is a mistake. Macrophages cannot fully degrade the oxidized LDL, so cholesterol accumulates in these cells, transforming them into **foam cells**. Foam cells die (necrosis), expelling their cytoplasm and cholesterol. In other words, the cells sent to remove the lipid core die and become part of the lipid core. Not only do the macrophages fail to process the LDL, but they also became necrotic and spill the LDL back into the lipid core AND exacerbate inflammation—increasing vascular permeability and monocyte recruitment—ensuring that more macrophages will enter the core. Now with necrotic cells trapped in the mix, it is a **necrotic lipid core**. The cycle repeats. Macrophages respond, fail, die, and release cytokines. As the responding macrophages die, they add to the necrotic lipid core. LDL and cholesterol continue to deposit from the circulation through the leaky endothelium, also adding to the necrotic lipid core.

While the macrophages are fighting and failing, **platelet** activation and adhesion to the dysfunctional endothelium result in the release of **platelet-derived growth factor (PDGF)**, which induces myofibroblast proliferation in the tunica media and migration of those myofibroblasts into the tunica intima. Platelet adhesion and activation are explored in detail in the Heme/Onc module. But the presence of PDGF informs the cells of the tunica media that they need to proliferate and keep the lipid core away from the vessel lumen, away from the blood. The first migration of the cells of the tunica media only serves to add to the lipid core, phagocytosing LDL, failing and dying as they do.

Arterial remodeling. The fatty streak starts to rise into the lumen. It is full of enough necrotic lipid core and proliferating myofibroblasts that it could compromise the lumen, but only a little. The vessel protects the integrity of the lumen through arterial remodeling. There is vasodilation and thinning of the tunica media—the affected vessel senses the increased resistance and seeks to restore the lower resistance by dilating as much as it can (remember, only arterioles can change their radius significantly, and atherosclerosis is a disease of large vessels). The thinning of the media accommodates the growing plaque so that the plaque does not enter the lumen. This is a good response, but it has its limitations.

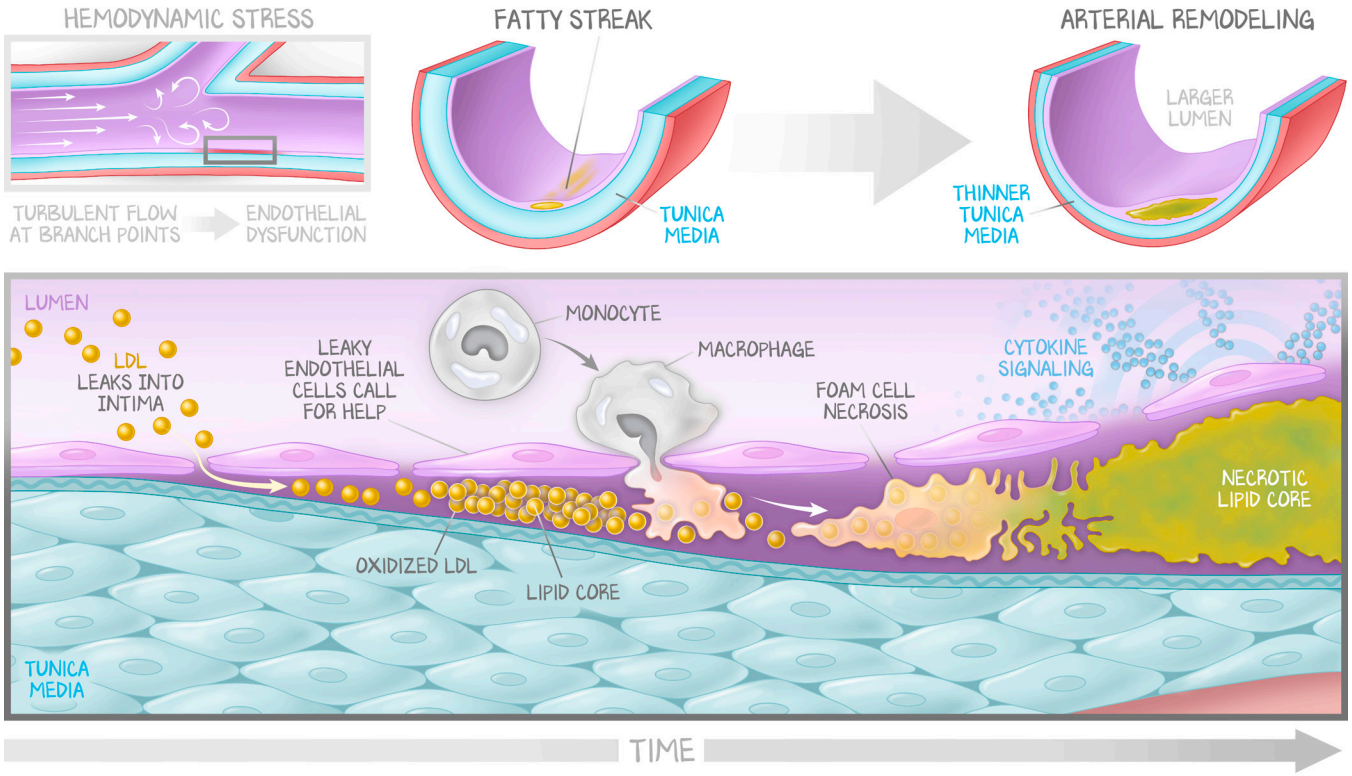

Figure 1.3: Fatty Streak to Arterial Remodeling
Hemodynamic stress causes turbulent flow and endothelial dysfunction, often at branch points. LDL leaks into the tunica intima, between the endothelial cells and the inner elastic lamina, forming a fatty streak. Eventually, the immune system senses a problem and dispatches macrophages to deal with the lipid core. As the macrophages fail (turning into foam cells and undergoing necrosis), the lipid core becomes a necrotic lipid core. The death of macrophages releases more inflammatory signals that make the endothelium leakier and summon more macrophages. As the lesion grows, the artery undergoes remodeling in an attempt to maintain the lumen diameter.

Complex atheroma. A complex atheroma is the step after arterial remodeling (no more remodeling can occur) and before stable plaque. It represents the immune system doing more than just throwing macrophages and myofibroblasts at the plaque. In truth, arterial remodeling is in response to a complex atheroma, and a complex atheroma can be categorized as a simple asymptomatic plaque (next). But we want you to learn these entities as discrete, separate stages, linking them to the underlying mechanism. Complex atheroma is a necrotic core covered by a fibrous cap that is well below critical stenosis. It is the first stage of atherosclerosis with intimal thickening—the lumen becomes impaired as the atheroma and the cells that contain it rise into the lumen. The cellular difference is that the adaptive immune system has noticed. No longer just neutrophils and macrophages, **T lymphocytes** join the necrotic core. They do so not as casualties in the fight against LDL but as the coordinators of that fight. The tunica intima is supposed to be just the endothelial cells, not all of this other stuff. The tunica media is supposed to be right up against the tunica intima. It is how the cells are programmed. Having had enough of this

foam cell failure, T lymphocytes enter the lipid core to set things straight. Smooth muscle cells won't be sacrificed to the necrotic core. Instead, they proliferate around the necrotic core, sealing it off from the adventitia and lumen—tunica media up against the tunica intima. Myofibroblasts from the tunica media proliferate and migrate over and around the necrotic lipid core and get up next to the endothelium. There they proliferate, creating a layer of cells to protect the necrotic lipid core from the artery's lumen. Myofibroblasts know how to lay down collagen, fibrillin, and elastin. In response to the necrotic core, they lay down mostly **collagen**. Collagen is hard, resistant, and inelastic. Fibrous tissue is hard, resistant, and inelastic. Thus, the combination of the cells themselves and the collagen they secrete is called a **fibrous cap**. When there are both a necrotic core and fibrous cap, the lesion in sum is called a **complex atheroma**. These cells and collagen take up space. The lesion now rises into the lumen, compromising the blood flow. Because there are a fatty (lipid) core and a fibrous cap, this complex atheroma is also referred to as a **fibrofatty plaque**.

The fibrous cap prevents the contents of the necrotic lipid core from entering the bloodstream. It does not prevent LDL, cholesterol, or macrophages from getting into the lipid core. The cycle continues, and the plaque grows.

Stable plaque. Fibrofatty plaque, fibrofatty atheroma, complex atheroma, and stable plaque are essentially all synonyms—fibrous cap and lipid core—and there is no cutoff for when a lesion goes from complex atheroma (begins to rise) to a stable plaque (advancing disease). As the plaque continues to grow, there is a progressive, eccentric (nonuniform, grows from only one side of the vessel) narrowing of the vessel. Two things matter at this point: will the plaque rupture and thrombose, and is the blood flow compromised? A **plaque rupture** would result in thrombosis and acute closure of the lumen (discussed below). Stable plaques do not readily rupture because the fibrous cap shields the lipid core from the circulation. If the plaque does not rupture, then the plaque can grow to **critical stenosis**. As the lesion grows to **70% stenosis** (only 30% of the lumen is open), symptoms can be provoked by increased demand of the tissue beyond the lesion. The symptoms depend on the organ the artery feeds, and because there is already limited blood flow but no symptoms at rest, symptoms are felt on exertion. In the coronaries, this would provoke angina; in the brain, transient ischemic attacks; in the legs, claudication.

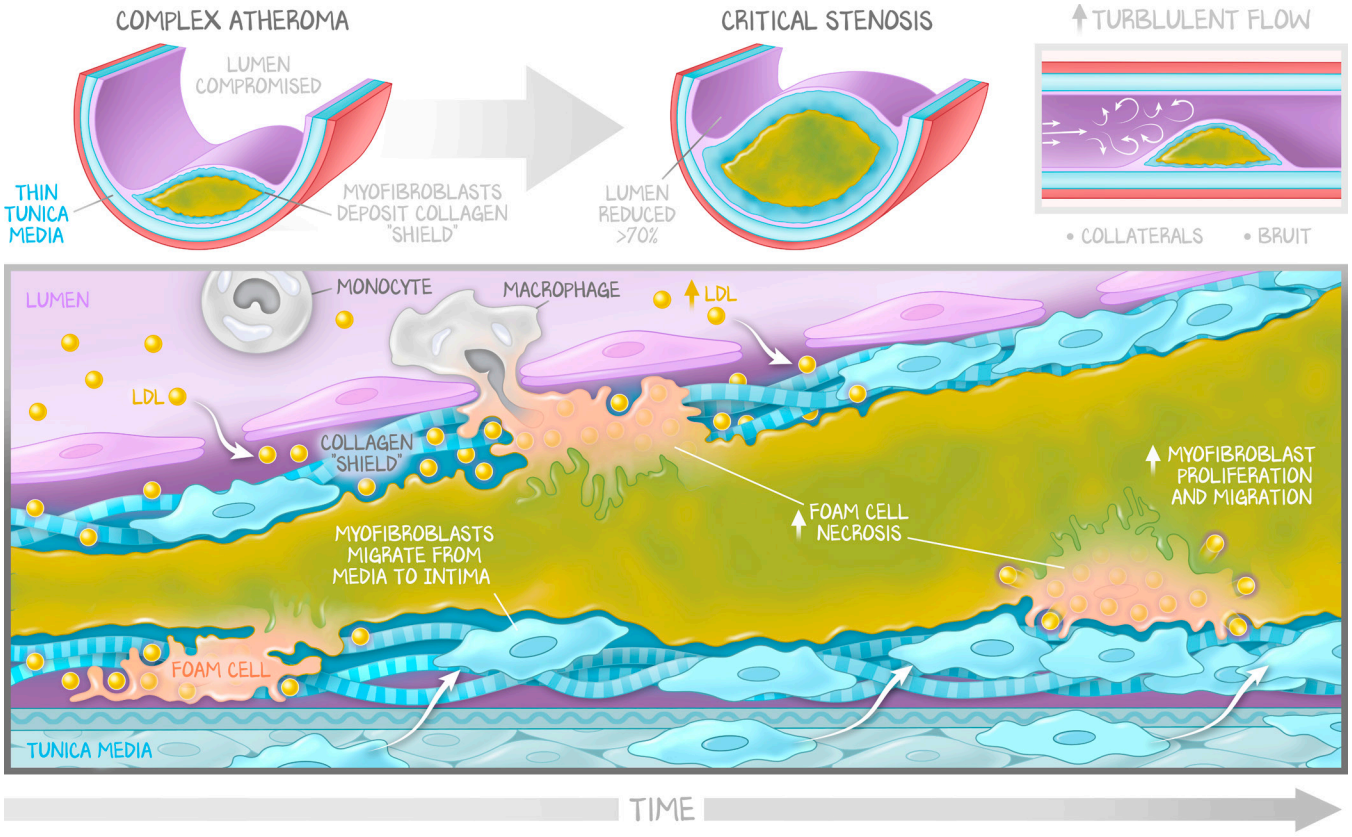

Figure 1.4: Arterial Remodeling to Critical Stenosis
A complex atheroma is a lipid core with a fibrous cap. A stable plaque is a complex atheroma as it begins to rise into the lumen. The lesion is eccentric (nonuniform) and continues to grow until critical stenosis is reached. The problem is that as the lesion gets larger, it occludes the vessel's lumen more, worsening the turbulent flow, and worsening the endothelial damage. And although the VSMCs help isolate the lipid core from the bloodstream, there is progressively less fibrous cap and more necrotic core as the lesion grows.

Because plaques develop slowly, **collateral circulation** may develop. This is angiogenesis. Small blood vessels grow around the lesion, anastomosing on either side. These "collaterals" can often be visualized with intravenous contrast at the time of diagnosis. What the contents of the lumen see is an intact endothelial cell layer, not the lipid core below. What the contents of the lumen feel is turbulent flow. Turbulence makes noise. Although you can't hear a coronary bruit, large arteries close to the skin's surface can succumb to the same atherosclerotic plaques as coronary vessels. Turbulence can be heard over an affected artery as a **bruit**. Turbulence also leads to further endothelial dysfunction. The bigger the plaque gets, the faster it grows.

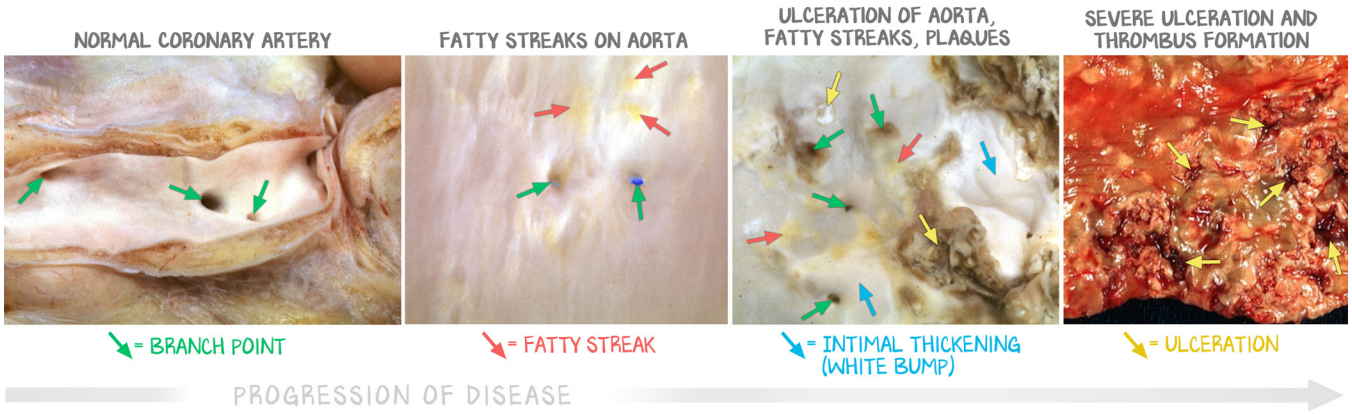

Figure 1.5: Progression of Atherosclerosis
A normal coronary artery is opened to reveal several branch points (the holes) and the white lining of the vessel. Use this to compare to the progression of disease. The rest of the photographs are of the aorta, taken from different autopsies and assembled to demonstrate disease progression. Fatty streaks appear yellow on the white background, occurring near branch points. As disease advances, there is intimal thickening (seen as bumps bulging into the lumen) and ulceration. Advancing disease continues to get uglier, and it gets harder to point out specific things. The final photograph has not been washed or fixed, demonstrating what a very diseased aorta looks like. The photograph is chaotic, with bumps all over the place, thrombus formation throughout, and ulcers everywhere.

Unstable plaque. The plaque will grow steadily as more lipid is accumulated in the necrotic core. The fibrous cap continues to contain the lipid core, but it also thins as the lipid core thickens. With repeated futile cycles and the accumulation of more lipid, the plaque doesn't just grow, it grows disproportionately—the core grows, but the cap doesn't. There are fewer VSMCs between the core and the lumen. The extracellular matrix of the fibrous cap is constantly remodeled. Collagen is degraded and resynthesized. But in the ongoing inflammation—in the presence of dying macrophages (which also release matrix metalloproteinases, but not on purpose)—there is a tipping point when degradation overtakes synthesis, termed **matrix degeneration**. The larger the plaque, the more necrosis, the thinner the fibrous cap, the more vulnerable to rupture. Worst of all, because the lumen is so narrowed, hemodynamic stressors (turbulence) continue to increase as the plaque increases in size. The VSMC:core ratio decreases, matrix degeneration increases, and turbulence increases. This is a feedforward effect. Increasing plaque size increases turbulent flow, increasing plaque size, etc. Turbulence from outside the core and matrix degeneration from within weaken the fibrous core and favor rupture.

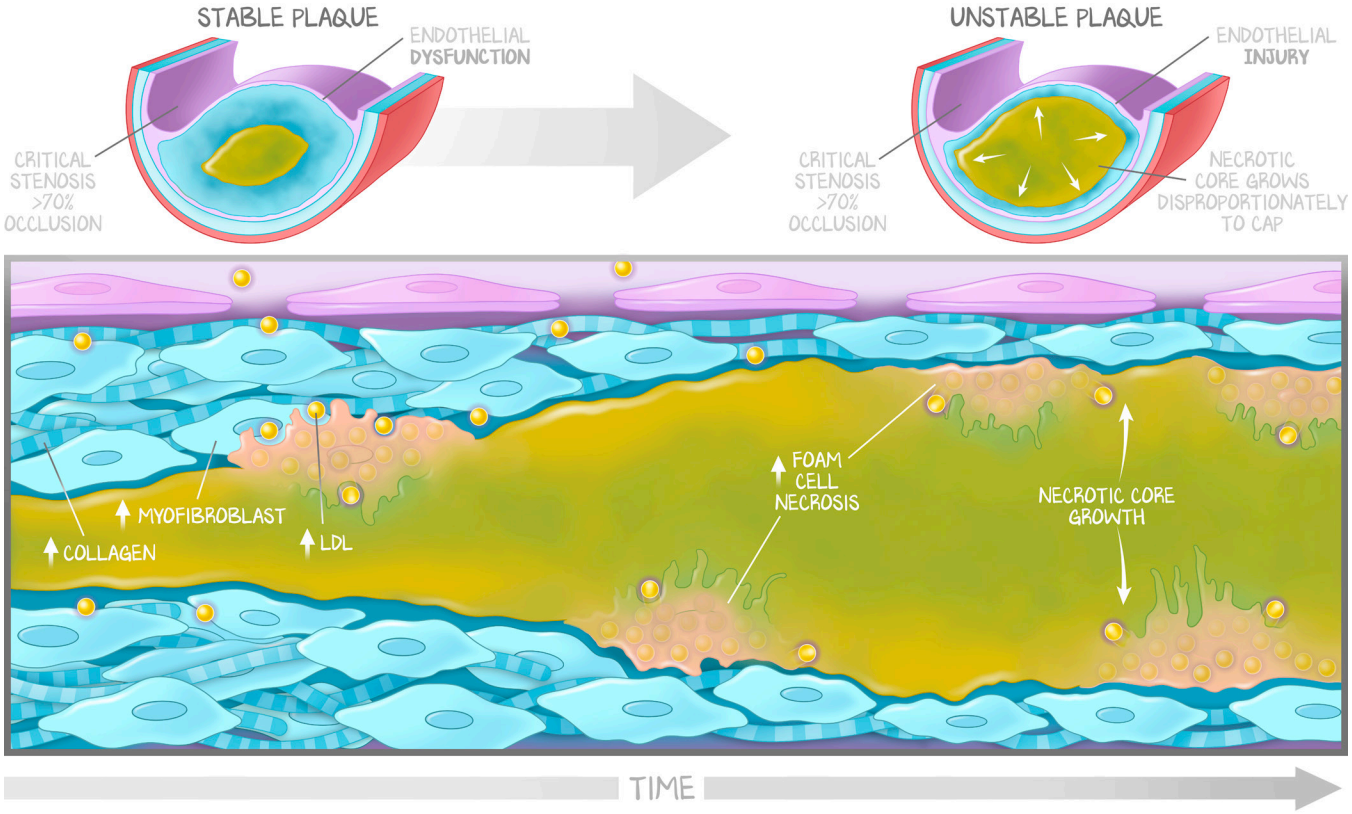

Figure 1.6: Stable and Unstable Plaques
A stable plaque has a large fibrous cap and not much necrotic core. As the disease continues, the lesion gets larger, and the endothelium endures increasing injury from worsening turbulent flow. The lesion grows because the necrotic lipid core increases in size. Simultaneously, the degradation of the fibrous cap means there is an ever-increasing necrotic core while there is also an ever-decreasing cap to core ratio.

Plaque Rupture and Thrombosis

Say "rupture and thrombosis" as if it were all one word. We want you to visualize: *if the fibrous cap ruptures and exposes the lipid core to the bloodstream* (rupture), *there will be total occlusion of the vessel* (thrombosis). Rupture and thrombosis take a stable plaque to a heart attack.

Fibrous cap rupture is a consequence of hemodynamic stress and matrix degeneration. When the fibrous cap ruptures, the necrotic lipid core is exposed to the bloodstream. The **necrotic lipid core** is **intensely thrombogenic**—if the cap breaks and the lipid core is exposed to the bloodstream, an acute platelet clot called a **thrombosis** forms. Clot, thrombosis, thrombus; these words are technically interchangeable but used to communicate two very different pathologies. In Heme/Onc, we expand on this concept of arterial platelet clots vs. venous factor thrombi—a distinction that is not only a Dustynism but also incredibly useful. Platelet arterial clots are treated with antiplatelets, whereas venous factor thrombi are treated with anticoagulation. In the Cardiac module, we have atherosclerosis and arterial platelet clots. The **larger the plaque**, the **larger the core**, the **smaller the cap**, and the **smaller the lumen**—all correspond to worsening disease.

Once critical stenosis is reached in a coronary vessel, there will be exertional symptoms—chest pain with exercise. There are three potential outcomes of critical stenosis: progression, rupture and thrombosis, and aneurysm. Progression is the continuation of plaque growth, the gradual worsening of the stenosis. This progresses slowly, gradually worsening the exertional symptoms (the patient will not be able to go as far

or as fast without symptoms). In Hemodynamics #3: *Aorta*, we saw that atherosclerosis could lead to aneurysm or dissection. Aneurysms of the coronary vessels don't have a specific presentation, although they may be found on angiography. In the Cardiac island, we only care about rupture and thrombosis—acute occlusion of a vessel that leads to a heart attack.

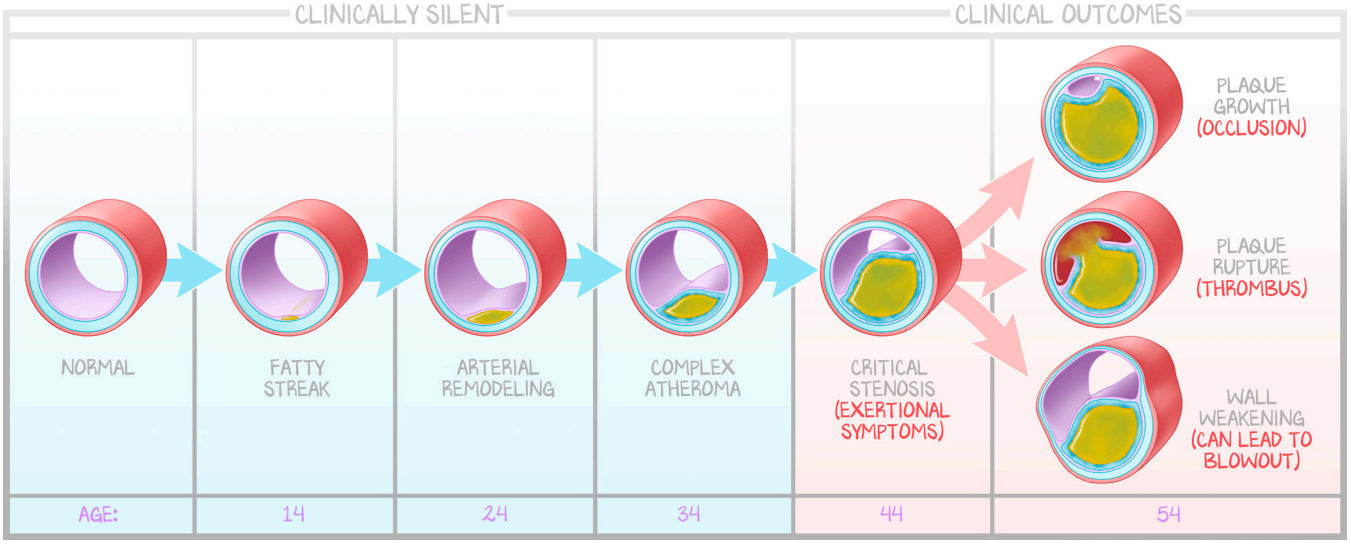

Figure 1.7: Continuation of the Plaque
The slow progression from normal artery to advanced vulnerable plaque. The advancing plaque causes no symptoms or disease. Once a critical diameter is reached, the clinical phase is realized.

Where to From Here?

LDL is the molecular culprit of atherosclerosis. We talk about lipid pharmacology, calling on what you learned in Biochemistry: Metabolism, in the next lesson. Stable plaques that narrow the lumen cause demand ischemia. We talk about the pathology of coronary demand ischemia in CAD #3: *Chronic Ischemic Heart Disease*, and the management of coronary demand ischemia in CAD #4: *Chronic Ischemic Heart Disease Pharmacology*. Plaque rupture results in supply ischemia, the pathogenesis of which we discuss in CAD #5: *Acute Coronary Syndrome,* and the treatment of which we discuss in CAD #6: *Pharmacology of ACS*.